atomic bombs in Japan. Among those men who were monitored there have been four deaths from leukaemia and one from multiple myeloma, making dose response analysis for these causes of very limited value. A qualitative classification of all participants into groups thought by the Ministry of Defence to have been exposed to different levels of radiation showed no particular relationships.

Since about 90% of the test participants are still alive these results and the future follow up are of much importance. The preferrred conclusion so far must surely be that some leukaemias, and probably multiple myelomas, have resulted from radiation exposure during the tests. This is a stronger conclusion than the authors are prepared to reach because of the lack of certainty in the findings. But earlier claims that other cancers have also increased among the test participants have no particular support from this study.

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Antisperm antibodies in infertility

One of the several unresolved problems of infertility is how much antisperm antibodies contribute to the problem.[1-3] Nor do we best know how to treat the infertility caused by antisperm antibodies, although various treatments are available.

Sperm are potentially immunogenic in men but are separated from the immune system by the blood-testis barrier. Autoimmunisation against sperm may occur if the barrier is breached by testicular trauma, vasectomy, tubal obstruction, or inflammation. Isoimmunisation against sperm might be expected to be common in sexually active women as sperm are recognised as foreign antigens, but immunosuppressive factors in semen,[4] the few sperm passing high into the uterus and tubes, and phagocytosis of sperm by macrophages[5] may discourage sensitisation. It remains to be seen whether direct intraperitoneal insemination, which bypasses these immunological defences, will cause isoimmunisation.[6]

Testing interactions between semen and cervical mucus is clinically useful in determining whether antisperm antibodies are contributing to the patient's infertility but depends on timing in the preovulatory phase. The simple postcoital test[7] and the controlled conditions of tests of sperm mucus penetration[8] and sperm mucus contact[9] may be helpful, but other causes of infertility must be excluded before attributing the infertility to antisperm antibodies.

Antibody tests are not widely available and are of uncertain clinical importance. The mixed agglutination reaction[10] or the tray agglutination test[2] may be used for screening, but the most useful assay is the immunobead method: washed sperm are incubated with commercially available immunoglobulin coated beads, which can then be seen linked to specific portions of motile sperm.[11] Serum and secretions can be tested by preliminary incubation with donor sperm, but in men direct testing of sperm is preferable.[12] High degrees of bead binding on more than 80% of sperm appear to be confined to infertile couples and men who have had vasectomies.[13]

There is reasonable evidence that certain antisperm antibodies are associated with reduced fertility when present in semen or cervical mucus. In couples with unexplained infertility the prevalence may be about 10%.[14-16] Several mechanisms have been proposed and they may work together. They include immobilisation of sperm in mucus[17]; stimulation of complement mediated cell lysis[13] or phagocytosis by macrophages[18]; interference with capacitation or acrosome reactions[19]; and defective interaction with the ovum.[20] Antibodies directed against sperm heads appear to affect all of these functions, whereas antibodies against tails only weakly affect mucus interactions.[13]

An effective treatment has not been established, and few current treatments have been tested in controlled trials. Use of condoms may reduce antibody titres in the woman, but the treatment's effectiveness is unsubstantiated. Corticosteroid immunosuppression has been advocated, and various regimens have been explored with mixed success.[21-24] Hendry has reported reductions in antibody titres in patients taking corticosteroids, but serious complications have occurred in a few patients.[25] Intrauterine insemination with washed sperm can produce pregnancies,[21 26] but since antibodies are difficult to clear from sperm by washing and since women with antibodies probably have them higher in the tract than simply the cervix[27] its value may be limited. The same problems limit the use of gamete intrafallopian transfer in female isoimmunisation, but it may be of value in male autoimmunisation.

In vitro fertilisation gives maximum control over the interaction between sperm and oocytes and antibody exposure. Standard in vitro fertilisation can work in isoimmunised women, but cleavage rates are reduced.[2] Washing the cumulus free of follicular fluid containing antibodies and using donor serum in the culture medium have improved cleavage rates.[28] Standard in vitro fertilisation also works with male autoimmunisation, but manipulations may further improve pregnancy rates. As techniques of gamete intrafallopian transfer and in vitro fertilisation improve they are likely to emerge as the best treatments for longstanding immunological infertility, but it is too early to assess their relative merits.

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1 Lilford RJ, Dalton ME. Effectiveness of treatment for infertility. *Br Med J* 1987;**295**:155-6.
2 Bronson R, Cooper G, Rosenfeld D. Sperm antibodies—their role in infertility. *Fertil Steril* 1984;**42**:171-83.
3 Mandelbaum SL, Diamond MP, de Cherney AH. The impact of antisperm antibodies on human infertility. *J Urol* 1984;**138**:1-8.
4 Price RJ, Roberts TK, Green D, Boettcher B. Anticomplementary activity in human semen and its possible importance in reproduction. *American Journal of Reproductive Immunology* 1984;**6**:92-8.
5 Mayer DL, Rimdusit S, Mishell DR. Sperm distribution and degradation in the human female reproductive tract. *Obstet Gynecol* 1970;**35**:831-40.
6 Forrler A, Dellenbach P, Nisand I, *et al*. Direct intraperitoneal insemination in unexplained and cervical infertility. *Lancet* 1986;ii:916-7.
7 Soffer Y, Marcus ZH, Bukovsky V, Caspi E. Immunological factors and postcoital tests in unexplained infertility. *Int J Fertil* 1976;**21**:89-95.
8 Kremer J. A simple sperm penetration test. *Int J Fertil* 1965;**10**:209-15.

9 Kremer J, Jager S. The sperm-cervical mucus contact test—a preliminary report. *Fertil Steril* 1976;27:335-40.
10 Jager S, Kremer J, Draaisma TvS. A simple method of screening for antisperm antibodies in the human male. *Int J Fertil* 1978;223:12-21.
11 Friberg J. A simple and sensitive moicro-method for demonstration agglutinating activity in serum from infertile men and women. *Acta Obstet Gynecol Scand (Suppl)* 1974;36:21-9.
12 Bronson RA, Cooper GW, Rosenfeld DL. Seminal fluid antisperm antibodies do not reflect those present on the sperm surface. *Fertil Steril* 1987;48:505-6.
13 Bronson RA, Cooper GW, Rosenfeld DL. Correlation between regional specificity of antisperm antibodies to the spermatozoa surfaces and complement—mediated sperm immobilization. *Am J Reprod Immunol Microbiol* 1982;2:222-4.
14 Haas GG Jr, Cines DB, Schreiber AD. Immunological infertility: identification of patients with antisperm antibody. *Fertil Steril* 1981;36:486-95.
15 Mathur S, Baker ER, Williamson HO, Derrick FC, Teague KJ, Fudenberg HH. Clinical significance of sperm antibodies in infertility. *Fertil Steril* 1981;36:486-95.
16 Witkin SS, Bongiovanni AM, Berkeley A, Ledger WJ, Toth A. Detection and characterisation of immune complexes in the circulation of infertile women. *Fertil Steril* 1984;42:384-8.
17 Kremer J, Jager S. Characteristics of anti-spermatozoal antibodies responsible for the shaking phenomenon with special regard to immunoglobulin class and antigen-reactive sites. *Int J Androl* 1980;3:143-52.
18 London SN, Haney AF, Weinberg JB. Macrophages and infertility—enhancement of human macrophage—mediated sperm killing by antisperm antibodies. *Fertil Steril* 1985;43:274-8.
19 Bronson R, Cooper G, Rosenfeld DL. Complement mediated effects of sperm head-directed human antibodies on the ability of human spermatozoa to penetrate zona-free hamster eggs. *Fertil Steril* 1983;40:91-9.
20 Mandelbraum SL, Diamond MP, de Cherney AH. Relationship of antisperm antibodies to oocyte fertilization and cleavage in in vitro fertilisation. *Fertil Steril* 1987;47:644-51.
21 Shulman S, Harlin B, David P, Reyniak JV. Immune infertility and new approaches to treatment. *Fertil Steril* 1978;29:309-13.
22 Hendry WF, Stedronska J, Paslaw J, Hughes L. The results of intermittent high dose steroid therapy for male infertility due to antisperm antibodies. *Fertil Steril* 1981;36:351-5.
23 Hargreave TB, Ecton R. Treatment with intermittent high-dose methylprednisolone or intermittent betamethasone for antisperm antibodies. *Fertil Steril* 1982;38:586-90.
24 De Almeida M, Feneux D, Rigaud C, Jouannet P. Steroid therapy for male infertility associated with antisperm antibodies. Results of a small randomized clinical trial. *Int J Androl* 1985;8:111-7.
25 Hendry WF. Treatment of antisperm antibodies. In: Hargreave TB, ed. *Male Infertility*. Berlin: Springer Verlag, 1983:280-96.
26 Kremer J, Jager S, Kiuken J. Treatment of infertility caused by antisperm antibodies. *Int J Fertil* 1978;23:270-6.
27 Allen NC, Herbert CM, Maxson WS, Rogers BJ, Diamond MP, Wentz AC. Intrauterine insemination: a critical review. *Fertil Steril* 1985;44:569-80.
28 Yovich JL, Stanger JD, Kay D, Boettcher B. In vitro fertilisation of oocytes from women with serum antisperm antibodies. *Lancet* 1984;i:369-70.

How does smoking harm the duodenum?

The relation between smoking and duodenal ulcer has often been examined, yet some reviewers take a sceptical view on whether smoking is important in duodenal ulcers[1] while others state that patients with duodenal ulcers should stop smoking.[2] The controversy has continued until recently,[3] but the best recent evidence is that smoking slows the healing of duodenal ulcers and encourages recurrence.[4,5] What is not clear is why smoking has these effects.

Contradictory answers have been given to the question of whether smoking increases gastric acid secretion. Intravenous nicotine does not increase acid secretion,[6] and patients with duodenal ulcers who smoke do not show any increase in basal secretion of acid or pepsin or in serum concentrations of pepsinogen I while smoking.[7] But chronic smoking is associated with significantly higher acid secretion after pentagastrin stimulation and increased serum concentrations of pepsinogen I.[7] Maximal acid output was increased in male but not female smokers with duodenal ulcers,[8] but after controlling for variables such as height and age the effect of smoking on acid secretion was no greater in patients with duodenal ulcers than in normal subjects.[9] Studies of the effect of smoking on duodenal pH have also produced conflicting results.[10,11]

Other possible explanations of how smoking affects duodenal ulcers have also come to grief. Neither smoking nor intravenous nicotine has been shown to affect the production of gastric mucus,[12] and in the duodenum both basal bicarbonate secretion and secretion after acid stimulation are unaltered by smoking.[13] The evidence that smoking increases bile reflux into the stomach from the duodenum[14] may explain the effects of smoking on gastric ulcer but not duodenal ulcer.[2]

Smoking has, however, been reported to reduce the amount of prostaglandin E_2 in gastric juice[15] and to inhibit prostaglandin synthesis in gastric mucosa.[16] These effects seem to be rapidly reversible, which means that if prostaglandin deficiency explains the effects of smoking on peptic ulcer then stopping smoking would be quickly beneficial.[16] Unfortunately, this hypothesis probably does not explain the effects of smoking on duodenal ulcer because prostaglandin production by duodenal mucosa seems to be unaffected by smoking.

Another way of investigating the effects of smoking on duodenal ulcers is to look at how smoking alters treatment. Smoking is thought to reduce the antisecretory activity of H_2 receptor antagonists[17] and to decrease their effects on nocturnal acidity—possibly because of reduced plasma concentrations of the drugs, which might be caused by increased gastric emptying.[18] Others, however, have found that smoking does not interfere significantly with the action of H_2 receptor antagonists.[19]

Although smoking might hamper treatment with antisecretory agents, it does not interfere with drugs that enhance mucosal defences. Thus healing rates and lengths of remission were significantly greater in smokers with duodenal ulcers treated with sucralfate than in those treated with cimetidine.[20] Smoking caused more frequent and earlier relapses in patients treated with ranitidine but had no effect on patients treated with colloidal bismuth.[21] Similarly, the ulcer healing properties of misoprostol, a derivative of prostaglandin E_1, were unaffected by cigarette smoking,[4] and the same has been claimed for enprostil, a derivative of prostaglandin E_2.[22]

It thus seems that the adverse effects of smoking on duodenal ulcers are overcome either by prostaglandin analogues or by drugs such as sucralfate and colloidal bismuth that stimulate endogenous prostaglandin production.[23] This fits with the evidence that smoking reduces prostaglandin synthesis in gastric mucosa if not in duodenal mucosa. It may be that in smokers with duodenal ulcers active smoking impairs prostaglandin release in the duodenum in response to an acid load, although basal prostaglandin generation is unchanged.

This is speculation, and more work must be done to elucidate how smoking harms the duodenum. There is no doubt, however, that patients who want their duodenal ulcers to heal and stay healed should stop smoking.

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1 Wormsley KG. Smoking and duodenal ulcer. *Gastroenterology* 1978;75:139-42.
2 McCarthy DM. Smoking and ulcers—time to quit. *N Engl J Med* 1984;311:726-8.
3 Barakat MH, Menon KM, Badawi AR. Cigarette smoking and duodenal ulcer healing. *Digestion* 1984;29:85-90.
4 Bauerfeind P, Popien J, Traber M, *et al.* Clinical perspectives of drugs inhibiting acid secretion: histamine H_2 antagonists. *Scand J Gastroenterol* 1986;21(suppl 125):42-8.